



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|  |           |   |
|--|-----------|---|
| (51) International Patent Classification <sup>6</sup> :<br><b>A61K 35/78</b>   | <b>A1</b> | (11) International Publication Number: <b>WO 00/00212</b><br>(43) International Publication Date: 6 January 2000 (06.01.00)   |
| <p>(21) International Application Number: PCT/US99/13893</p> <p>(22) International Filing Date: 22 June 1999 (22.06.99)</p> <p>(30) Priority Data:<br/>60/090,930 28 June 1998 (28.06.98) US<br/>09/261,941 3 March 1999 (03.03.99) US</p> <p>(71) Applicant (for all designated States except US): NUTRACORP SCIENTIFIC, INC. [US/US]; Suite 300, 2980 Beverly Glen Circle, Los Angeles, CA 90077 (US).</p> <p>(72) Inventors; and<br/>(75) Inventors/Applicants (for US only): SHELL, William, E. [US/US]; Suite 300, 2980 Beverly Glen Circle, Los Angeles, CA 90077 (US) JARMEL, Mark, E. [US/US]; Suite 300, 2980 Beverly Glen Circle, Los Angeles, CA 90077 (US).</p> <p>(74) Agent: CHARTOVL, Alex, Alin, Gump, Strauss, Hauer &amp; Feld, LLP, Suite 400, 1333 New Hampshire Avenue, N.W., Washington, DC 20006 (US).</p>  |           | <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b><br/>With international search report.</p> |
| <p>(54) Title: PROMOTING NITRIC OXIDE AND CYCLIC GMP ACTIVITY</p>  |           |   |
| <p>(57) Abstract</p> <p>Methods and compositions for promoting nitric oxide (NO) and/or cGMP activity in a subject. A precursor for nitric oxide, such as arginine, is orally administered together with an agonist for NO, including thioamino acids, substituted mono or polyphenol antioxidants and plant extracts that promote endothelium-dependent relaxation, to synergistically enhance NO activity and thereby cGMP activity. cGMP activity is further enhanced by concomitant administration of phosphodiesterase inhibitor, including inhibitors specific to type V phosphodiesterase, such as sildenafil, and non-specific inhibitors, particularly xanthines, such as theobromine. The formulations are used in the treatment of NO and/or cGMP insufficiency, and particularly conditions involving the cardiovascular, pulmonary and reproductive systems, such as erectile dysfunction or deficiency in luteinizing hormone releasing hormone.</p> |           |   |

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

|    |                          |    |  |    |  |    |                          |
|----|--------------------------|----|--|----|--|----|--------------------------|
| AL | Albania                  | ES | Spain                                    | LS | Lesotho                                      | SI | Slovenia                 |
| AM | Armenia                  | FI | Finland                                  | LT | Lithuania                                    | SK | Slovakia                 |
| AT | Austria                  | FR | France                                   | LU | Luxembourg                                   | SN | Senegal                  |
| AU | Australia                | GA | Gabon                                    | LV | Larvia                                       | SZ | Swaziland                |
| AZ | Azerbaijan               | GB | United Kingdom                           | MC | Monaco                                       | TD | Chad                     |
| BA | Bosnia and Herzegovina   | GE | Georgia                                  | MD | Republic of Moldova                          | TG | Togo                     |
| BB | Barbados                 | GH | Ghana                                    | MG | Madagascar                                   | TJ | Tajikistan               |
| BE | Belgium                  | GN | Guinea                                   | MK | The former Yugoslav<br>Republic of Macedonia | TM | Turkmenistan             |
| BF | Burkina Faso             | GR | Greece                                   | ML | Mali   | TR | Turkey                   |
| BG | Bulgaria                 | HU | Hungary                                  | MN | Mongolia                                     | TT | Trinidad and Tobago      |
| BJ | Benin                    | IE | Ireland                                  | MR | Mauritania                                   | UA | Ukraine                  |
| BR | Brazil                   | IL | Israel                                   | MW | Malawi                                       | UG | Uganda                   |
| BY | Belarus                  | IS | Iceland                                  | MX | Mexico                                       | US | United States of America |
| CA | Canada                   | IT | Italy                                    | NE | Niger  | UZ | Uzbekistan               |
| CF | Central African Republic | JP | Japan                                    | NL | Netherlands                                  | VN | Viet Nam                 |
| CG | Congo                    | KE | Kenya                                    | NO | Norway                                       | YU | Yugoslavia               |
| CH | Switzerland              | KG | Kyrgyzstan                               | NZ | New Zealand                                  | ZW | Zimbabwe                 |
| CI | Côte d'Ivoire            | KP | Democratic People's<br>Republic of Korea | PL | Poland                                       |    |                          |
| CM | Cameroon                 | KR | Republic of Korea                        | PT | Portugal                                     |    |                          |
| CN | China                    | KZ | Kazakstan                                | RO | Romania                                      |    |                          |
| CU | Cuba                     | LC | Saint Lucia                              | RU | Russian Federation                           |    |                          |
| CZ | Czech Republic           | LI | Liechtenstein                            | SD | Sudan  |    |                          |
| DE | Germany                  | LK | Sri Lanka                                | SE | Sweden                                       |    |                          |
| DK | Denmark                  | LR | Liberia                                  | SG | Singapore                                    |    |                          |
| EE | Estonia                  |    |  |    |  |    |                          |

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

## 5 SPECIFICATION

## 10 PROMOTING NITRIC OXIDE AND CYCLIC GMP ACTIVITY

## BACKGROUND OF THE INVENTION

15 This invention relates generally to agents for promoting activity of nitric oxide (NO) and cyclic GMP. Many health conditions, such as hypertension, coronary artery disease, erectile dysfunction and asthma, involve insufficient levels of NO and/or cyclic GMP. Previous approaches to the treatment of such conditions have utilized pharmaceutical agents whose effectiveness for a given  
20 individual decreases over time. Additionally, these pharmaceutical agents have known undesirable side effects and are incapable of correcting the underlying insufficient production of NO and/or cyclic GMP involved in a variety of disease processes. Accordingly, there is a need for an effective means for promoting the synthesis of nitric acid and cyclic GMP within the body while minimizing side  
25 effects.

NO is produced naturally in the body and carries out important physiological functions, many of which are mediated by its ability to activate guanylyl cyclase to thereby enhance production of cyclic guanylyl monophosphate (cGMP).

30 Additionally, NO has functions in the body independent of cGMP pathways, including promoting the release of hormones in the body. In particular, NO enhances the release of luteinizing hormone releasing hormone in the brain and

functions in this respect as the primary mediator of sexual receptivity in the female.

There has been increasing attention to the value of enhancing NO and cGMP activity in order to treat a variety of disorders, including conditions involving the cardiovascular, pulmonary and urogenital systems. One specific application of this invention relates to the treatment of erectile dysfunction in men. As men age the responsiveness of the neurochemical mechanisms that control erection decreases and the incidence of erectile dysfunction increases. The pharmaceutical agent sildenafil has been shown to increase the levels of cGMP, thereby promoting the production of erections in men. Sildenafil, a type V phosphodiesterase inhibitor that is specific to the phosphodiesterase that breaks down cGMP, has been found to have sufficient activity to be clinically efficacious. However, sildenafil and other pharmaceutical agents utilized to promote the activity of cyclic GMP and/or the production of erections have known undesirable side effects. Additionally, sildenafil is a costly prescription medication. Accordingly, there is a need for an effective means for promoting the activity of cGMP while minimizing side effects and reducing cost to the consumer.

Nitric oxide is known to stimulate the release of cGMP and thus enhances its activity in the body. Arginine is a precursor for nitric oxide (NO) and the substrate of nitric oxide synthase (NOS) in the production of NO. Administration of arginine has been proposed for stimulating NO production, thereby to enhance cGMP. Cooke et al. U.S. Patent 5,428,070 describes oral administration for long-term effect in raising NO level for treatment of atherogenesis and restenosis. For a more rapid effect, intravascular administration is employed instead of oral. In the case of intravascular administration, Cooke proposes the use of antioxidants (e.g. sulfhydryl-containing compounds and thiols) along with the arginine to reduce degradation of endogenous NO. However, the effectiveness of arginine as proposed by Cooke is very limited, at best, requiring an oral dose of as much as four grams to be effective.

Theophylline is known to be use in treating pulmonary conditions. However, it has not been found useful in treating cardiovascular or urogenital conditions.

5 The thioamino acids, cysteine and methionine, and monophenols and polyphenols in chemically isolated form and as constituents of plant extracts, are known to be agonists for NO and they are believed to function by scavenging or decomposing oxygen-derived free radicals that inhibit the formation of NO. The effect of various plant extracts as endothelium-dependent relaxants, mediated by enhancement of NO production thereby to increase cGMP, was studied and  
10 reported by Fitzpatrick et al., "Endothelium-Dependent Vasorelaxation Caused by Various Plant Extracts," Fitzpatrick et al., *J. of Cardiovascular Pharmacology*, 26:90-95, Raven Press Ltd, New York. The plant extracts were prepared and tested for endothelium-dependent relaxation (EDR) under a detailed protocol (referred to herein as "Fitzpatrick Protocol") by measuring the relaxation (or contraction)  
15 imparted by diluted samples to an aortic ring precontacted by phenylephrine to arrive at an EDR value that is the percentage of relaxation imparted. A wide variety of extracts were tested and the EDR values for these extracts ranged from negative values (contraction) to a high of 98.1%. Fitzpatrick et al. suggest the increased consumption of plant products in general and those exhibiting NO-  
20 enhancing properties in particular, for enhancement of NO production. However, none of the phenols, either isolated or in plant extract form, have been demonstrated to have sufficient activity for promoting NO or cyclic GMP to be clinically useful for this purpose.

25 Phosphodiesterase inhibitors are known to enhance cGMP by decreasing its rate of breakdown in the body by phosphodiesterase. Non-specific phosphodiesterase inhibitors, and particularly methyl xanthines, are known to have phosphodiesterase inhibitory activity but not to a sufficient degree to be clinically useful in treating most conditions involving NO and/or cGMP insufficiency. Theophylline is known to be useful in treating pulmonary

conditions. However, neither theophylline or the other xanthines have been found useful for treating cardiovascular or urogenital conditions.

5

## SUMMARY OF THE INVENTION

This invention has the object of increasing the activity of nitric oxide and/or cGMP in the body for achieving desired effects and thus provides methods and compositions for enhancing mechanisms endogenous to the body that promote production of NO and enhance cGMP activity. This invention also has the object of enabling use of agents not considered either prescription or non-prescription drugs to achieve these effects. This invention also enables use of readily available, low cost, safe agents found in the ordinary diet, to promote NO production and provide enhanced activity of cGMP at reduced dosage to minimize cost and the possibility of side effects. This invention has the further object of promoting the neurovascular mechanisms endogenous to the body that produce erections in the male and the endogenous hormonal mechanisms that produce sexual receptivity in the female. Additionally, cardiovascular, urogenital and pulmonary functions responsive to NO may be beneficially promoted in accordance with this invention.

This invention is based upon the discovery that concomitant administration of a nitric oxide precursor in the arginine pathway and selected agonists for NO that scavenge oxygen radicals, surprisingly act synergistically to maximize NO production and thereby to enhance cGMP activity. The NO agonists include thiols (particularly thioamino acids or precursors thereof such as glutathione), substituted monophenol and polyphenol antioxidants and plant extracts having endothelium-dependent relaxation (EDR) activity. With this combination the various desirable physiological effects of NO in the body may be promoted, including those mediated by cGMP and those that are independent of cGMP.

In a further important aspect of this invention where the desired NO activity is mediated through cGMP, a phosphodiesterase inhibitor is administered concomitantly with the NO precursor and NO agonist. With this combination, phosphodiesterase inhibitors that are otherwise ineffective for treating cardiovascular and urogenital conditions, such as the non-specific inhibitors, and particularly the methyl xanthines, may be rendered clinically useful for these purposes. Phosphodiesterase inhibitors that are clinically effective alone, such as the type V phosphodiesterase-specific inhibitor, sildenafil, may be employed in what would otherwise be subclinical doses with adequate effect.

A further aspect of this invention is the use as the NO agonist in the formulations of this invention of natural plant derived substances having the ability to act as NO agonists and particularly monophenol and polyphenol-containing plant substances. The extract to be employed in the formulations are from plant parts that have EDR values, as determined by the Fitzpatrick protocol, of at least 50%, preferably at least 75% and most preferably at least 90%. Cinnamon has been found to be particularly effective in the combinations of this invention for potentiating the erection-promoting effects of arginine. Advantageously, the plant substances used are in the form of comminuted and dried plant parts, teas or liquid extracts from the plant parts.

A further aspect is the use, as NO agonists in the formulations of this invention, of sulfur-containing amino acids, methionine, cystine or cysteine (thioamino acids) or substituted mono and polyphenols.

A further aspect is the use in the formulations of the invention of a methyl xanthine, heretofore not considered as clinically efficacious as a phosphodiesterase inhibitor for treating cardiovascular and urogenital conditions, and particularly caffeine, theophylline and theobromine. Particularly advantageous is theobromine in the form of cocoa.

A yet further aspect of the invention is the use of sildenafil as the phosphodiesterase inhibitor, at dosage levels that would be subclinical, together with the NO agonist and NO precursor that render the dosage efficacious, thereby

reducing the possibility of side effects, tolerance, or attenuation of its effectiveness and lowering the cost of the formulation.

As another feature to insure effectiveness of the compositions of this invention, they are desirably administered to the subject on an empty stomach and concomitant intake by the subject of foodstuffs is desirably restricted. Such intake may adversely affect absorption by the subject of the active agents. In particular, to avoid competitive absorption, the concomitant intake by the subject of amino acids, other than the NO precursors administered, is desirably restricted to an amount less than about 50% by weight of the substrate amino acids administered. Preferably, concomitant intake of such other amino acids is completely excluded. Similarly, to prevent interference with absorption of NO precursors, concomitant intake of fiber is desirably limited to about 10% by weight of NO precursor amino acids administered and is preferably excluded completely.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The following description illustrates the manner in which the principles of the invention are applied but is not to be construed as limiting the scope of the invention. In this invention a nitric oxide precursors in the arginine pathway and an agonist for NO, which may be a thioamino acid, a monophenol or polyphenol or an EDR-active plant extract, are administered orally concomitantly, based on the discovery that such co-administration results in an unexpected degree of enhancement in the level of NO in the subject. Additionally, in this invention a phosphodiesterase inhibitor utilized for increasing cyclic GMP activity may be administered orally concomitantly with the NO precursor and NO agonist, based on the further discovery that co-administration thereof will cause an unexpected degree of enhancement of cyclic GMP activity in the subject. The enhancement of cGMP activity is manifested in the vasodilatation and other



effects on the host and is believed to result from the combined increased production of these messengers in the host, due to the enhanced production of NO in the host caused by the NO precursor and NO agonist administered together, and the reduction in breakdown of the messengers by phosphodiesterase by the phosphodiesterase inhibitor. Enhancement of cGMP activity in the context of this invention is intended to comprehend either or both increasing the production of cGMP and sustaining the level of cGMP in the subject by retarding its reuptake due to enzymatic breakdown.

Pharmaceutical agents produce their effects by either activating or inhibiting mechanisms that are already present in the body. They, therefore, attempt to emulate actions normally produced by the body's intrinsic homeostatic mechanisms. All pharmaceuticals that are foreign to the body have associated undesirable side effects since synthetic drugs imperfectly interact with the body's regulatory mechanisms. Side effects are further promoted by the nonselective distribution of drugs throughout the bloodstream. These pharmaceuticals thus may affect each organ and body system in unknown and potentially undesirable ways. This invention has the advantage of permitting the administration of naturally occurring agents, namely amino acids and plant-derived substances that are normally utilized by the body's intrinsic homeostatic mechanisms. Administering nutrients normally utilized by the body along with substances long utilized as food stuffs desirably decreases the occurrence of side effects. Thus, this invention advantageously emulates effects produced by synthetic pharmaceutical agents on various mechanisms mediated by NO and/or cGMP, with reduced risk of side effects.

As will be treated in detail herein, the naturally occurring agents may be employed in this invention in pure form, e.g. exogenous material synthesized or derived from animal or vegetable sources, particularly purified extracts. Concomitant administration of a carbohydrate and particularly sugar, dextrin, starch and the like, is desired in order to cause release of insulin to thereby enhance cGMP activity.

For enhancing NO production for effects independent of cGMP the NO precursor and NO agonist are administered concomitantly for producing those effects, which particularly include enhancing the release of hormones, such as lutenizing hormone releasing hormone in the brain. This procedure may be  
5 employ to relieve hormone deficiencies by stimulating their production.

Concomitant administration of the NO precursor and NO agonist is useful, as well, for enhancing NO production for effects mediated by c-GMP. However, in this invention the activity of c-GMP may further enhanced by the concomitantly administering with the NO precursor and NO agonist a phosphodiesterase  
10 inhibitor. This combination is advantageous for the purpose of ameliorating cGMP deficiencies and thereby optimizing mechanisms mediated by cGMP. A c-GMP deficiency includes any condition in which the production cGMP is less than optimal. cGMP deficiencies result in less than optimal regulation of body functions leading to a wide variety of conditions and disorders. These are the  
15 conditions and disorders that may be treated under this invention. This invention thus may be employed for a wide range of applications involving cGMP deficiencies and/or for creating or maintaining desired physiological effects or states mediated by cGMP.

In this invention arginine and agents that enhance cGMP activity are  
20 administered for the purpose of ameliorating cGMP deficiency and thereby optimizing mechanisms mediated by cGMP. cGMP deficiency includes any condition in which the production of cGMP or its release is less than optimal. cGMP deficiency results in less than optimal regulation of body functions leading to a wide variety of conditions and disorders. These are the conditions and  
25 disorders that may be treated under this invention. This invention thus may be employed for a wide range of applications involving cGMP deficiency and/or for creating or maintaining desired physiological effects or states mediated by cGMP.

These applications include use in treating vascular insufficiency, vascular resistance and other vascular disorders, hypertension and pulmonary conditions.  
30 However, the oral compositions of this invention are particularly suitable,

particularly because of their quick action, increased blood flow within 30 minutes to hour, for treating erectile dysfunction and especially for improving erectile function in subjects experiencing age-related decline in neurovascular mechanisms that mediate the production of erections.

5       The NO precursors employed in this invention are those that are useful in and follow the arginine pathway, i.e. they are converted in the body to a form of arginine suitable as a substrate for NOS. This will include arginine, itself, and its physiologically acceptable salts, such as hydrochloride and glutamate salts. It also includes precursor peptides (i.e. poly-L-arginine) and naturally occurring  
10       sources such as protamine. Arginine is the preferred precursor.

      The monophenol and polyphenol NO agonists employed in this invention include the well-known class of antioxidants, the flavinoids, and non-flavinoid antioxidants. These are monophenolic and polyphenolic compounds that have a phenol group with one or more substituents having a carbon linkage with the  
15       benzene ring and typically the substituents comprise functional groups, such as carboxyl or formyl groups, on the benzene ring or on an alkyl or alkyne group on the benzene ring. The substituent may also constitute a non-aromatic ring having one or more carbon linkage to the benzene ring of the phenolic moiety, particularly in the case of polyphenols. The monophenolic and polyphenolic  
20       compounds may be in the form of their physiologically acceptable salts, hydrates, adducts, mineral chelates and esters. The non-flavinoids include the polyphenol oligomers tetrahydroxy benzene, pentahydroxy benzene (quercitol) and hexahydroxy benzene (inositol). The also include the monphenol agonists of the following classes: the benzoic acid derivatives (e.g. vanillic, gallic and  
25       protocatechuic acids and hydrolyzable tannins), benzaldehyde derivatives (e.g. vanillin and syringaldehyde) cinnamic acid and its derivatives (e.g. p-coumaric, perulic, chlorogenic and caffeic acids) and cinnamaldehyde and its derivatives (coniferaldehyde and sinapaldehyde).

      The flavinoids include the flavinols (e.g. quercetin, rutin, kaempferol, and  
30       myricetin), the anthocyanins (e.g. cyanin, delphinin, petunin and malvin),

leucocyanidin, leucocyanidol, resversotrol, marchantins, carnosol, carnosic acid, oleuropin, the proanthocyanidins (e.g. pycnogenol) and the flavin-3-ols (e.g. catechin, epicatechin, galliccatechin, epigallocatechin, procyanidins and condensed tannins), including oligomers (e.g. dimer through heptamers), salts and esters thereof.

Many of the foregoing substituted mono and polyphenols are found in and derivable from plants, e.g. catechin, quercetin, resveratrol and leucocyanidol from red wine. Thus, if desired, one or more specific antioxidant phenols may be isolated and from plant sources and employed, in purified form, as a plant extract in this invention, as will be discussed. Alternatively, if desired, individual phenols may be synthesized and used in that form.

However, it is particularly convenient and advantageous to utilize in this invention as an NO agonist processed vegetable matter from vegetable sources that are EDR-active. Plant source EDR activity commonly from concentrations of endogenous substituted mono and polyphenols and thus to some extent the plant extract category in this invention overlaps with the mono and polyphenol NO agonist category. However, other EDR-activity agents may be present in such extracts, either alone or in addition to a phenol component.

The presence and amount of a positive EDR activity will vary not only with each plant species, but with each specific part, e.g. pulp or "meat," seeds, leaves, skins, berries, flowers, etc., of a particular species. However, suitable plant parts may be selected by use of a straight-forward screening procedure. To test a candidate plant or plant part, an extract may be prepared and tested in accordance with the protocol set forth in the J. Cardiovascular Pharmacology report of Fitzpatrick et al. referenced in the background of this invention, which paper is incorporated herein by reference.

Desirable sources include plant sources with sufficient EDR activity that extracts prepared therefrom and tested in accordance Fitzpatrick et al have a substantial positive endothelium-dependent relaxation (EDR) activity and desirably an ability to induce an value endothelium-dependent relaxation of 50%.

or higher. Plant sources having a positive EDR value lower than 50%. For example, plant sources with an EDR activity as low as 20%, may be useful, if processed to sufficiently concentrate the level of phenols and other EDR-active agents in the plant source, e.g. by evaporation or solvent extraction.

- 5 A wide variety of plant sources can be employed including those reported by Fitzpatrick et al. with substantial positive EDR values. The more desirable sources include the following:

|    |                   |    |                          |
|----|-------------------|----|--------------------------|
|    | cinnamon          | 30 | rosemary                 |
|    | bilberry          |    | garlic                   |
| 10 | cranberry         |    | <i>Eugenia uniflora</i>  |
|    | lima bean         |    | red wine extract         |
|    | corn              |    | lemon, orange,           |
|    | blackeye peas     | 35 | and grapefruit           |
|    | red cabbage       |    | pulp                     |
| 15 | guava pulp        |    | lemon, orange,           |
|    | apple skin        |    | and grapefruit           |
|    | red apple pulp    |    | peel                     |
|    | plum skin         | 40 | leaves of <i>Eugenia</i> |
|    | plum pulp         |    | <i>uniflora</i>          |
| 20 | peanut skin       |    |                          |
|    | peanut meat       |    |                          |
|    | eggplant skin     |    |                          |
|    | pecan skin        |    |                          |
|    | walnut skin       |    |                          |
| 25 | grape skin        |    |                          |
|    | grape seeds       |    |                          |
|    | tea leaves (green |    |                          |
|    | and black)        |    |                          |
|    | sassafras         |    |                          |

Of the foregoing, the most preferred plant sources include cinnamon, guava pulp, green tea, plum pulp and skin, red apple pulp and skin, peanut skin, bilberry, cranberry and eggplant skin and leaves of *Eugenia uniflora*. The suitability of additional plant sources can be ascertained by utilizing the test protocol of Fitzpatrick et al.

The selected vegetable source can be processed in various ways. These include preparation of a water, water/alcohol, ethyl acetate or other solvent extract, extracting plant liquid from the source and making a dried product. (particularly for dried plant substances (e.g. tea, spices) make infusion by conventional methods. Additionally, the dried product, particularly dried spices, such as cinnamon, may be crushed and/or comminuted and used in that form in the compositions of this invention.

For preparing a plant liquid it is desirable to first masticate the selected plant part (e.g. mince and grind) to form pulp. The pulp may be dried and comminuted for use in the formulations of this invention or liquefied to serve additionally as a liquid base for liquid composition forms of this invention. In the case of vegetables, seeds and other dense plant materials it is desirably to use mild heat (e.g. at the boiling point of water) to help liberate the liquids, together with the phenols and or other EDR-active agents. The mash thus prepared is then filtered, desirably with compression.

To prepare a dried product, masticate the desired plant part before or after dehydrating, dehydrate in a conventional manner, preferably at moderate temperature or under partial vacuum. Alternatively, a plant liquid or extract may first be prepared and this liquid processed to powder form by dehydration and comminution. Additionally a more concentrated plant liquid or liquid extract can be prepared by distilling off water, preferably under partial vacuum.

As used herein, plant extracts are intended to include plant-derived products processed as in the foregoing description, including those that retain fiber,

carbohydrates, water, and other inert constituents of the plant part and those that are not prepared in concentrated form. They are inclusive of products that are plant parts that have simply been prepared to a liquid, aggregate or powder form that will permit them to be processed into dosage forms with the other  
5 components of this invention.

The phosphodiesterase inhibitors employed in this invention include both those which have proven to be effective for treating one or more cardiovascular and urogenital conditions, such as sildenafil, zaprinast and siguazelan and those that are not effective alone for these purposes. The clinically effective inhibitors  
10 are specific to and potent inhibitors of type V cGMP-specific phosphodiesterase enzyme. The inhibitors that are clinically effective are advantageously used in this invention in doses that are subclinical if used alone.

Xanthines constitute a class of phosphodiesterase inhibitors that are not specific to the type V cGMP-specific phosphodiesterase enzyme. They are known  
15 to be capable of promoting activity of cyclic GMP to a limited degree but are not effective for treating cardiovascular and urogenital conditions. Combining one or more xanthines, with a precursor for NO in combination with one or more of the NO agonists of this invention will promote cyclic GMP sufficiently to for treating cardiovascular and urogenital conditions with safe doses of the  
20 individual agents.

The xanthines may be used in the form of their free compounds or as their salts, adducts or other derivatives, for example citrated caffeine, theophylline ethylenediamine, theophylline sodium acetate, sodium glycinate, the choline salt, the theophylline derivatives theophylline megumine and dyphylline,  
25 theobromine calcium salicylate, sodium acetate or sodium salicylate.

A particularly suitable form of xanthines for use in this invention are those that are derived from natural sources. Cocoa provides a unique combination of the xanthines theobromine and caffeine in a form that is normally easily ingested and tolerated by the subject.

Infusions of caffeine from coffee beans and of caffeine and theophylline from tea leaves may be employed as a natural source of these xanthines, either in liquid form as coffee and tea, or in dried extract form, alone or, more conveniently, in composition with the neurotransmitter precursor. Caffeinated soft drinks,  
5 chocolate, guarana, ephedra, mate' and other food or herb sources may be employed.

As used in this invention the NO precursors and NO agonists function synergistically in enhancing NO production. At the threshold dosage levels and even at the preferred levels of both the NO precursors and agonists used together  
10 in this invention, the amount of either would typically be insufficient to appreciably stimulate NO if used alone. This synergism may taken into account in selecting appropriate dosage levels for both the NO precursors and the NO agonists. Desirably, the dosages for the NO precursor and NO agonist utilized together in this invention are amounts that are sufficient together to stimulate  
15 production of NO. To establish an optimum dose levels for a particular combination of precursor and agonist, it may be useful to test a series of dosage levels, start with higher dosage levels of both and then incrementally reduced dosages of each component until the NO activity begins to drop appreciably. This may be conveniently done utilizing one of the commercially available  
20 instruments for measuring NO levels in exhaled breath and in body fluids. The following general dosage ranges for NO precursors and agonists for use in this invention will provide further guidance.

The desired single dose range for this purpose for the NO precursor arginine and its salts is typically from about 10 to 1,000 milligrams or higher if tolerated by  
25 the subject. A typical dose of arginine being 500 milligrams in formulations of this invention. These dosage ranges are applicable for promoting NO production with the NO agonists in this invention. They are also applicable where phosphodiesterase inhibitors are additionally administered in accordance with this invention to further enhance cyclic GMP activity.



The appropriate dosage for monophenol and polyphenol NO agonists in the formulations of this invention for either synthetically derived substituted mono and polyphenols or mono and polyphenols as a concentrated or purified extract isolated from a plant source, a single dose of about 10 to 500 mg will normally be appropriate but dosages up to 1 gram are higher may be employed to insure maximum activity. Such dosages are generally well tolerated.

For EDR-active plant extracts where the EDR active agents are not fully isolated from the constituents of the plant part, whether or not the activity is from endogenous phenols, the dosage amounts will be correspondingly higher. For the dried plant materials as NO agonists, a dosage range may extend from about 100 mg to 1 gram, with typical dose from 300 to 800 mg but higher dosage above 1 gram can be appropriate to insure maximum activity. For liquid extracts of plant materials and for plant liquids a dosage of from about 25 ml to 300 ml or higher is normally appropriate. Here, again, higher dosages up to 1 liter or higher may be used to insure adequate effect and such doses are normally tolerated easily. Where the plant liquid or liquid extract has been concentrated, the dosage levels may be decreased proportionally.

The thioamino acids include methionine and cysteine and the oxidation product of cysteine in the body, cystine, and their physiologically acceptable salts, hydrates, adducts, mineral chelates and esters. They are desirably utilized as NO agonists in the formulations of this invention at dosage levels of from about 20 to 800 mg. A preferred dosage range is from 100 to 300 mg.

For further promoting cGMP activity by utilizing phosphodiesterase inhibitors that are non-specific to type V cGMP-specific phosphodiesterase, the dosage level will vary depending upon the activity level of the inhibitor. In general, the xanthines are employed in dosage ranges sufficient to further promote cyclic GMP activity. In the case of some xanthines extremely high doses are desirably avoided to limit undesired side effects. Theobromine may be administered in a dosage of from 1 mg. to 2 grams or higher. Caffeine may be administered in a dose of from 1 to 200 mg or higher if tolerated by the subject.

Theophylline may be administered in a dose of from 1 to 200 mg or higher if tolerated by the subject. Cocoa may be administered in a dose of 1 mg. to 10 grams or higher for an appropriate dose of xanthines, with a preferred dose being 500 to 800 milligrams. Somewhat higher doses of these xanthines may be employed  
5 with some subjects without undue discomfort.

For formulations of this invention that employ sildenafil and other inhibitors that are specific to type V cGMP-specific phosphodiesterase, the dosage of such inhibitors is desirably at or below the threshold clinical activity level for the inhibitor. For sildenafil or its homologues and analogs, non-esterified or  
10 esterified with other organic acids or salts thereof, the dosage is desirably at or below about 20 mg and preferably in the range of about 3 to 15 mg.

The active agents of this invention may be administered orally separately, or for assurance of appropriate proportions and dosages as well as for convenience, they are administered together in the same composition. Moreover, it has been  
15 found that there is a considerable attenuation of effectiveness if the interval between administration of the components is too great. Thus, whether administered separately or in the same composition, the agents are advantageously administered concomitantly, and preferably simultaneously. By concomitant administration is meant administration of each component within a  
20 reasonably short time of the other, desirably within a half-hour and preferably, within 15 minutes or a shorter period.

The dosage forms for administration separately or in the same composition may be any of the conventional forms, including carbonated beverages, capsules, caplets, chewable wafers, tablets, liquid suspensions, powders and the like.  
25 Xanthine dosages may take the form of chocolate preparations, cocoa drinks, and cola drinks containing caffeine, either separate or incorporating the other desired ingredients.

The compositions in the form of powders or liquids may be packaged in multiple dosage quantities with instructions to the user to extract therefrom for  
30 ingestion appropriate individual dosage amounts, e.g. a teaspoonful. However,

the compositions are desirably prepared in discrete units, e.g. prepackaged beverages, capsules, wafers, etc., which each contain the appropriate dosage amounts of NO precursors, NO agonists and/or phosphodiesterase inhibitor for a single dose as discussed above. The compositions may include the usual carriers,  
5 in fillers, excipients, flavorings and adjuvants in addition to active agents.

To insure effectiveness of the compositions, they are desirably administered to the subject on an empty stomach and concomitant intake by the subject of foodstuffs is desirably restricted. Typically the composition is administered at least an hour after the subject has eaten. To avoid competitive absorption, the  
10 concomitant intake by the subject of amino acids, other than the NO precursors administered, is desirably restricted to an amount less than about 50% by weight of the substrate amino acids administered. Preferably, concomitant intake of such other amino acids is completely excluded. Similarly, to prevent interference with absorption of NO precursors, concomitant intake of fiber is desirably limited to  
15 about 10% by weight of NO precursor amino acids administered and is preferably excluded completely.

A single dose daily of the compositions of this invention should be effective to raise the basal level of cyclic GMP activity. One or two doses daily is recommended for the treatment of cardiovascular and urogenital conditions  
20 responding to enhanced cyclic GMP activity, e.g. angina. If desired for improving erectile function, administration 30 to 60 minutes before sexual activity is recommended. The effects of the formulations of this invention normally should be sufficiently potent that their effects can be evaluated after first or second. The following examples illustrate various embodiments of the invention.

25

### Example 1

A formulation was prepared such that a single dose comprised arginine 500 mg, n-acetyl cysteine 300 mg, choline 175 mg, vitamin C 100 mg, vitamin E 100  
30 mg, caffeine 25 mg, biotin 300 mcg, cocoa 1,000 mg and sugar 3,000 mg. The

blended powder was mixed in water and administered on an empty stomach to three adult men in their 40s and 50s. Each of these individuals reported significantly enhanced quality of erections. An alternative formulation was prepared in which molybdenum 150 mcg was substituted for the n-acetyl cysteine.

5 This alternative formulation was administered on an empty stomach to the three men in their 40s and 50s. Each of the three men reported enhancement of erections similar to the first formulation. These formulations are best administered when a subject has an empty stomach, preferably at least one hour after eating. It is also desirable to administer the formulation approximately 30-60

10 minutes prior to sexual activity.

### Example 2

A formulation was prepared such that a single dose comprised arginine 500

15 mg, cocoa 500 mg, cinnamon 450 mg, sucrose 300 mg, choline 175 mg, cysteine 100 mg, glutamic acid 100 mg, vitamin C 100 mg, vitamin D 100 IU, vitamin E 100 IU, glycine 25 mg, manganese 5 mg, folic acid 400 mcg, biotin 300 mcg, and molybdenum 150 mcg. These ingredients were then portioned into gelatin capsules, and administered on an empty stomach to 4 adult males in their 40s and

20 50s. Each of these individuals reported significantly enhanced quality of their erections. This formulation is best administered as an Example 1.

### Example 3

25 A formulation may be prepared comprising arginine 500 mg, cinnamon 500 mg, cocoa 500 mg, and sugar 1,000 mg. These ingredients may be administered as a single dose in the form of a powder to be added to a cup of coffee or portioned into gelatin capsules. This formulation is best administered as an Example 1.

30

### Example 4

A formulation may be prepared comprising arginine 500 mg, cinnamon 500 mg, caffeine 25 mg, and sugar 500 mg. These ingredients may be portioned into gelatin capsules and administered as in Example 1.

5

#### Example 5

A formulation may be prepared comprising arginine 500 mg, cinnamon 500 mg and sildenafil 12.5 mg. This formulation may be portioned into gelatin capsules and is best administered as in Example 1.

10

#### Example 6

A formulation may be prepared arginine 500 mg, queracetin 500 mg, and sildenafil 12.5 mg. This formulation is best administered as in Example 1. This formulation allows reduced dosages of sildenafil to be effective in the treatment of erectile dysfunction, thereby desirably reducing costs and the potential risk of side effects.

15

20

#### Example 7

A formulation may prepared comprising arginine 500 mg, myricetin 500 mg, and sildenafil 12.5 mg. This formulation is best administered as in Example 1. These formulation allow sildenafil to be administered in reduced dosages compared to those typically utilized to produce vasodilatation. Thus, the potential risk of side effects associated with these pharmaceutical agents is greatly reduced by this invention.

25

30

#### Example 8

A formulation may be prepared comprising arginine 500 mg, OligoProCyanidin 200 mg, and caffeine 25 mg. OligoProCyanidin is a product sold by Jarrow Formulas, Los Angeles, California, and it is a 100:1 grape seed extract

containing 25% anthocyanosides This formulation may be portioned into gelatin capsules and is best administered as in Example 1.

#### Example 9

5

A formulation may be prepared comprising 500 mg arginine, 200 mg Bilberry 100:1, cocoa 500 mg, and sugar 500 mg. Bilberry 100:1 is a product sold by Jarrow Formulas, Los Angeles, California, and it is a mixture, at a weight ratio of 2 to 5, of a 100:1 bilberry extract containing 25% anthocyanosides and grape skin extract with 30% polyphenols. This formulation may be portioned into gelatin. This product may be administered with a single dose daily for cardiovascular and urogenital conditions responding to enhanced cyclic GMP activity or as described in Example 1 specifically for improving erectile function.

15

#### Example 10

A formulation may be prepared and used as in Example 9 except that Bilberry 100:1 is replaced with 500 mg. queracetin. This product may be used as described in either Example 1 or 9.

20

#### Example 11

A formulation may be prepared and used as in Example 9 except that Bilberry 100:1 is replaced with 500 mg. of dried garlic powder. The garlic powder is prepared by mincing and grinding fresh garlic cloves into a mash which is dried under warm air flow and then pulverized to a powder. This product may be used as described in either Example 1 or 9

30

#### Example 12

A formulation may be prepared and used as in Example 9 except that Bilberry 100:1 is replaced with 300 mg. of methionine. This product may be used as described in either Example 1 or 9

5

### Example 13

A formulation may be prepared comprising arginine 500 mg, 6 oz. of dealcoholized red wine and 25 mg of caffeine. This formulation allows the health-promoting benefits and flavor of red wine to be provided without alcohol and at reduced calories. Alternatively, 400 mg of a dry extract of red wine solids containing 30% by weight of polyphenols may be substituted for the dealcoholized red wine thereby allowing the formulation to be administered in capsule form.

This formulation is best administered as in either Example 1 or 9.

As can be seen from the foregoing, the synergistic combinations of the invention allow reduced doses of the individual components to be used to achieve the desired effects. The reduced doses decrease side effects caused by the large doses heretofore necessary to achieve the desired effects. Our invention allows enhanced activity of cyclic GMP, to be achieved without requiring the utilization of pharmaceuticals. Our invention allows these desired effects to be achieved at dosage levels of neurotransmitter precursors that are considered safe by regulatory authorities. Previous attempts to use certain of the components in isolation were either ineffective or required dosages which caused side effects.

Although the description above contains many specificities, these should not be construed as limiting the scope of the invention but as merely providing illustrations of some of the presently preferred embodiments of this invention. Various other embodiments and ramifications are possible within it's scope.

## CLAIMS

1. A composition for promoting NO and/or cGMP activity in a subject which  
5 comprises at least one precursor for NO selected from arginine and a precursor of arginine and at least one agonist for NO selected from a thioamino acid, a substituted mono or polyphenol antioxidant and an EDR-active plant extract, the amount of precursor and the amount of agonist being sufficient together to stimulate production of NO.
- 10 2. A composition as in claim 1 and wherein the NO precursor is selected from arginine, physiologically acceptable salts, hydrates, adducts, and mineral chelates thereof, poly-L-arginine and protamine.
3. A composition as in claim 1 and wherein the NO agonist comprises a  
15 thioamino acid selected from methionine, cysteine, cystine and their physiologically acceptable salts, hydrates, adducts, mineral chelates and esters.
4. A composition as in claim 1 and wherein the NO agonist comprises a  
20 monophenol or polyphenol antioxidant selected from physiologically acceptable monophenolic and polyphenolic compounds having a phenol moiety which has at least one substituent moiety having a carbon linkage with the benzene ring of the phenol moiety.
5. A composition as in claim 4 and wherein the NO agonist is a substituted  
monophenol or polyphenol antioxidant extracted from a plant source.
6. A composition as in claim 4 and wherein the monophenol or polyphenol is  
selected from catechin, quercetin, resveratrol and leucocyanidol.
- 25 7. A composition as in claim 1 and wherein the NO agonist comprises a plant extract of a plant part having substantial EDR activity.
8. A composition as in claim 7 and wherein the plant extract is prepared from a plant part that, as tested in accordance with the Fitzpatrick protocol, will induce an endothelium-dependent relaxation of greater than 50%.



9. A composition as in claim 8 and wherein the NO agonist comprises a plant extract of a plant or plant part selected from cinnamon, guava pulp, green tea, plum pulp and skin, red apple pulp and skin, peanut skin, bilberry, cranberry and eggplant skin and leaves of *Eugenia uniflora*.
- 5 10. A composition as in claim 1 and wherein the composition further comprises a phosphodiesterase inhibitor in an amount effective to enhance cGMP activity in the subject.
11. A composition as in claim 10 and wherein the phosphodiesterase inhibitor is non-specific to type V cGMP-specific phosphodiesterase.
- 10 12. A composition as in claim 11 and wherein the phosphodiesterase inhibitor comprises a xanthine.
13. A composition as in claim 12 and wherein the xanthine comprises theobromine.
14. A composition as in claim 13 and wherein the theobromine comprises from  
15 about 1 mg. to 2 grams per dose.
15. A composition as in claim 12 and wherein the xanthine is in the form of cocoa.
16. A composition as in claim 12 and wherein the xanthine comprises caffeine.
17. A composition as in claim 10 and wherein the phosphodiesterase inhibitor  
20 comprises an inhibitor specific to type V cGMP-specific phosphodiesterase.
18. A composition as in claim 17 and wherein the dosage level of the inhibitor specific to type V cGMP-specific phosphodiesterase is at or below the threshold clinical activity therefor when utilized alone.
19. A composition as in claim 17 and wherein the phosphodiesterase inhibitor  
25 comprises sildenafil.
20. A composition as in claim 1 in unit dosage form and wherein the NO precursor comprises between about 10 mg. and 1 gram per dose.
21. A composition as claim 1 in unit dosage form in which the content of carbohydrates is no more than 6 grams of carbohydrates per dose and the content

of amino acids other than said substrate amino acids is no more than about 50% by weight of the NO precursor amino acids.

22. A composition for promoting cGMP activity in a subject which comprises at least one precursor for NO selected from arginine, physiologically acceptable salts, hydrates, adducts, and mineral chelates thereof, poly-L-arginine and protamine, at least one agonist for NO comprising an EDR-active extract and a xanthine, the amount of precursor and the amount of agonist being sufficient together to stimulate production of NO and the amount of xanthine being effective to enhance cGMP activity in the subject.
23. A composition as in claim 22 and wherein the xanthine comprises theobromine.
24. A composition as in claim 22 and wherein the xanthine is in the form of cocoa.
25. A composition as in claim 22 and wherein the plant extract is prepared from a plant part that, as tested in accordance with the Fitzpatrick protocol will induce an endothelium-dependent relaxation of greater than 50%.
26. A composition as in claim 22 and wherein the EDR-active extract is prepared from a plant or plant part selected from cinnamon, bilberry, cranberry, lima bean, corn, blackeye peas, red cabbage, guava pulp, apple skin, red apple pulp, plum skin, plum pulp, peanut skin, peanut meat, eggplant skin, pecan skin, walnut skin, grape skin, grape seeds, tea leaves (green and black), sassafras, rosemary, garlic *Eugenia uniflora*, red wine extract and lemon, orange, and grapefruit pulp and peel.
27. A composition as in claim 22 in unit dosage form and wherein the NO precursor comprises between about 10 mg. and 1 gram per dose.
28. A method for promoting NO and/or cGMP activity in a subject which comprises concomitantly administering to the subject at least one precursor for NO selected from arginine and a precursor of arginine, in a dose that is effective to enhance production of nitric oxide in the subject, and at least one agonist for NO selected from a thioamino acid, a substituted mono or polyphenol

antioxidant and an EDR-active plant extract, the precursor and the agonist being administered in amounts that together are sufficient to stimulate production of NO.

29. A method as in claim 28 and wherein the subject is a female having a deficiency in lutenizing hormone releasing hormone.

30. A method as in claim 28 and wherein the subject has an NO or cGMP insufficiency.

31. A method as in claim 28 and wherein the subject is a male having an erectile dysfunction.

32. A method as in claim 3 and wherein the NO precursor is selected from arginine, physiologically acceptable salts, hydrates, adducts, and mineral chelates thereof, poly-L-arginine and protamine.

33. A method as in claim 32 and wherein the NO agonist comprises a thioamino acid selected from methionine, cysteine, cystine and their physiologically acceptable salts, hydrates, adducts, mineral chelates and esters.

34. A method as in claim 32 and wherein the NO agonist comprises a monophenol or polyphenol antioxidant selected from physiologically acceptable monophenolic and polyphenolic compounds having a phenol moiety which has at least one substituent moiety having a carbon linkage with the benzene ring of the phenol moiety.

35. A method as in claim 32 and wherein the NO agonist is an EDR-active extract of a plant part that, as tested in accordance with the Fitzpatrick protocol, will induce an endothelium-dependent relaxation of greater than 50%.

36. A method as in claim 35 and wherein the extract comprises a monophenol or polyphenol antioxidant.

37. A method as in claim 36 and wherein the substituted monophenol or polyphenol antioxidant is selected from catechin, myricetin, quercetin, resveratrol and leucocyanidol.

38. A method as in claim 32 and wherein the NO precursor and NO agonist are administered to the subject orally on an empty stomach and including the further

step of restricting the concomitant intake by the subject of amino acids, other than NO precursor amino acids, to an amount less than 50% by weight of the substrate amino acids administered and of carbohydrates, to an amount of less than 6 grams.

- 5 39. A method as in claim 32 and including the concomitant administration to the subject of a phosphodiesterase inhibitor in an amount effective to enhance cGMP activity in the subject.
40. A method as in claim 39 and wherein the phosphodiesterase inhibitor is non-specific to type V cGMP-specific phosphodiesterase.
- 10 41. A method as in claim 41 and wherein the phosphodiesterase inhibitor comprises a xanthine.
42. A method as in claim 39 and wherein the phosphodiesterase inhibitor comprises a phosphodiesterase inhibitor that is specific to type V cGMP-specific phosphodiesterase.
- 15 43. A method as in claim 42 and wherein the dosage level of the inhibitor specific to type V cGMP-specific phosphodiesterase is at or below the threshold clinical activity therefor when utilized alone.
44. A method as in claim 42 and wherein the phosphodiesterase inhibitor comprises sildenafil.
- 20 45. A method as in claim 32 and wherein the NO precursor, NO agonist and phosphodiesterase inhibitor are administered to the subject orally on an empty stomach and including the further step of restricting the concomitant intake by the subject of amino acids, other than NO precursor amino acids, to an amount less than 50% by weight of the substrate amino acids administered and of
- 25 carbohydrates, to an amount of less than 6 grams.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/13893

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 35/78

US CL :424/195.1

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/195.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No.                 |
|-----------|--|---------------------------------------|
| X,P       | US 5,891,459 A (COOKE et al) 06 April 1999, abstract, col. 4, lines 54-67, col. 7, lines 20-67, col. 8, lines 1-67, col. 9, lines 16-25, col. 10, lines 18-26. | 1 - 5 , 7 , 8 , 1 0<br>20,28,30-36,39 |
| X,P       | US 5,904,924 A (GAYNOR et al) 18 May 1999, abstract, col. 3, lines 34-58, col. 4, lines 34-65  | 1-9, 20,28 32-37                      |

☐

Further documents are listed in the continuation of Box C.

☐

See patent family annex.

|   |  |
|---|--|
| * Special categories of cited documents:  | * later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  |
| *A* document defining the general state of the art which is not considered to be of particular relevance  | *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone   |
| *B* earlier document published on or after the international filing date  | *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | *A* document member of the same patent family  |
| *O* document referring to an oral disclosure, use, exhibition or other means  |  |
| *P* document published prior to the international filing date but later than the priority date claimed  |  |

Date of the actual completion of the international search

02 AUGUST 1999

Date of mailing of the international search report

20 OCT 1999

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231  
Facsimile No. (703) 305-3230

Authorized officer

ANGELA N. TRAFTON

Telephone No. (703) 308-0196

JOYCE BRIDGERS  
PARALEGAL SPECIALIST  
CHEMICAL MATRIX

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/13893

## B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, CA

plant extract, amino acids, erectile dysfunction, arginine, nitric oxide, cGMP, antioxidant, phosphodiesterase inhibitor, xanthine, sildenafil, green tea, bilberry, cranberry, grape



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|  |  |  |  |
|--|--|--|--|
| (51) International Patent Classification <sup>6</sup> :<br><b>A61K 35/78</b>   |  | <b>A1</b>  | (11) International Publication Number: <b>WO 00/00212</b>      |
|  |  |  | (43) International Publication Date: 6 January 2000 (06.01.00) |
| (21) International Application Number: PCT/US99/13893  |  | (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). |  |
| (22) International Filing Date: 22 June 1999 (22.06.99)  |  | <b>Published</b><br><i>With international search report.</i>   |  |
| (30) Priority Data:<br>60/090,930 26 June 1998 (26.06.98) US<br>09/261,941 3 March 1999 (03.03.99) US  |  |  |  |
| (71) Applicant (for all designated States except US): NUTRACORP SCIENTIFIC, INC. [US/US]; Suite 300, 2980 Beverly Glen Circle, Los Angeles, CA 90077 (US).   |  |  |  |
| (72) Inventors; and<br>(75) Inventors/Applicants (for US only): SHELL, William, E. [US/US]; Suite 300, 2980 Beverly Glen Circle, Los Angeles, CA 90077 (US). JARMEL, Mark, E. [US/US]; Suite 300, 2980 Beverly Glen Circle, Los Angeles, CA 90077 (US).  |  |  |  |
| (74) Agent: CHARTOVE, Alex; Akin, Gump, Strauss, Hauer & Feld, LLP, Suite 400, 1333 New Hampshire Avenue, N.W., Washington, DC 20036 (US).   |  |  |  |
| (54) Title: PROMOTING NITRIC OXIDE AND CYCLIC GMP ACTIVITY   |  |  |  |
| (57) Abstract<br><p>Methods and compositions for promoting nitric oxide (NO) and/or cGMP activity in a subject. A precursor for nitric oxide, such as arginine, is orally administered together with an agonist for NO, including thioamino acids, substituted mono or polyphenol antioxidants and plant extracts that promote endothelium-dependent relaxation, to synergistically enhance NO activity and thereby cGMP activity. cGMP activity is further enhanced by concomitant administration of phosphodiesterase inhibitor, including inhibitors specific to type V phosphodiesterase, such as sildenafil, and non-specific inhibitors, particularly xanthines, such as theobromine. The formulations are used in the treatment of NO and/or cGMP insufficiency, and particularly conditions involving the cardiovascular, pulmonary and reproductive systems, such as erectile dysfunction or deficiency in luteinizing hormone releasing hormone.</p> |  |  |  |

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

|    |                          |    |  |    |  |    |                          |
|----|--------------------------|----|--|----|--|----|--------------------------|
| AL | Albania                  | ES | Spain                                    | LS | Lesotho                                      | SI | Slovenia                 |
| AM | Armenia                  | FI | Finland                                  | LT | Lithuania                                    | SK | Slovakia                 |
| AT | Austria                  | FR | France                                   | LU | Luxembourg                                   | SN | Senegal                  |
| AU | Australia                | GA | Gabon                                    | LV | Latvia                                       | SZ | Swaziland                |
| AZ | Azerbaijan               | GB | United Kingdom                           | MC | Monaco                                       | TD | Chad                     |
| BA | Bosnia and Herzegovina   | GE | Georgia                                  | MD | Republic of Moldova                          | TG | Togo                     |
| BB | Barbados                 | GH | Ghana                                    | MG | Madagascar                                   | TJ | Tajikistan               |
| BE | Belgium                  | GN | Guinea                                   | MK | The former Yugoslav<br>Republic of Macedonia | TM | Turkmenistan             |
| BF | Burkina Faso             | GR | Greece                                   | ML | Mali   | TR | Turkey                   |
| BG | Bulgaria                 | HU | Hungary                                  | MN | Mongolia                                     | TT | Trinidad and Tobago      |
| BJ | Benin                    | IE | Ireland                                  | MR | Mauritania                                   | UA | Ukraine                  |
| BR | Brazil                   | IL | Israel                                   | MW | Malawi                                       | UG | Uganda                   |
| BY | Belarus                  | IS | Iceland                                  | MX | Mexico                                       | US | United States of America |
| CA | Canada                   | IT | Italy                                    | NE | Niger  | UZ | Uzbekistan               |
| CF | Central African Republic | JP | Japan                                    | NL | Netherlands                                  | VN | Viet Nam                 |
| CG | Congo                    | KE | Kenya                                    | NO | Norway                                       | YU | Yugoslavia               |
| CH | Switzerland              | KG | Kyrgyzstan                               | NZ | New Zealand                                  | ZW | Zimbabwe                 |
| CI | Côte d'Ivoire            | KP | Democratic People's<br>Republic of Korea | PL | Poland                                       |    |                          |
| CM | Cameroon                 | KR | Republic of Korea                        | PT | Portugal                                     |    |                          |
| CN | China                    | KZ | Kazakstan                                | RO | Romania                                      |    |                          |
| CU | Cuba                     | LC | Saint Lucia                              | RU | Russian Federation                           |    |                          |
| CZ | Czech Republic           | LI | Liechtenstein                            | SD | Sudan  |    |                          |
| DE | Germany                  | LK | Sri Lanka                                | SE | Sweden                                       |    |                          |
| DK | Denmark                  | LR | Liberia                                  | SG | Singapore                                    |    |                          |
| EE | Estonia                  |    |  |    |  |    |                          |